DEPARTMENT OF THE AIR FORCE
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23 NOV 2016

MEMORANDUM FOR SGVT
ATTN: CAPT TIMOTHY A. SOEKEN

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your poster, entitled **Evaluation of Quantitative Pupillometry for Detection of Intracranial Pressure Changes** presented at **North American Neuro-Ophthalmology Society 2017 Annual Meeting, Washington D.C., January 1-6, 2017** in accordance with MDWI 41-108, has been approved and assigned local file #**16397.**

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

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Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
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PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

TO:	FROM: Author's Name, Rank, Grade, Office Symbol	PROTOCOL NUMBER:
Clinical Research Division/SGVU (59 MDW/SGVU)	Timothy A. Soeken, Capt, O-3, Ophthalmology	H-34685

PROTOCOL TITLE - ***[NOTE: For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.]***
Evaluation of Quantitative Pupillometry for Detection of Intracranial Pressure Changes

1. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED
Evaluation of Quantitative Pupillometry for Detection of Intracranial Pressure Changes

2. FUNDING RECEIVED FOR THIS STUDY? ☒ YES ☐ NO **FUNDING SOURCE:** National Space and Biomedical Research Institute

3. IS THIS MATERIAL CLASSIFIED? ☐ YES ☒ NO

4. IS THIS MATERIAL SUBJECT TO ANY LEGAL RESTRICTIONS FOR PUBLICATION OR PRESENTATION THROUGH A COLLABORATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA), MATERIAL TRANSFER AGREEMENT (MTA), INTELLECTUAL PROPERTY RIGHTS AGREEMENT ETC.? ☐ YES ☒ NO
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I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401_IP AND 59 MDWI 41-108. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.

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6. COMMENTS

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The abstract is approved.

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The views expressed are those of the authors and do not reflect the official views or policy of the Department of Defense or its Components.

The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CRR 219 and DoDI 3216.02_AFI 40-402, Protection of Human Subjects in Biomedical and Behavioral Research.

Evaluation of Quantitative Pupillometry for Detection of Intracranial Pressure Changes

Tim Soeken MD, Al Alonso, Roy Haas PhD, Aaron Grant MD, Jonathan Clark MD, Dorit Donoviel PhD, and Eric M. Bershad MD

Abstract

Background: There is a need to develop non-invasive methods to monitor the intracranial pressure (ICP) in space and on earth. In traumatic brain injury patients, elevated ICP is associated with pupils that are poorly reactive to light as measured by quantitative pupillometry. However, it is unknown whether pupillary reactivity will decrease when ICP is elevated but without brain injury or cerebral edema, such as in patients with idiopathic intracranial hypertension, or healthy subjects undergoing physiological maneuvers to transiently elevate the ICP.. We sought to determine the pupillary reactivity related to maneuvers that elevate ICP including head down tilt, breath holding and Valsalva maneuver in healthy subjects and patients with idiopathic intracranial hypertension.

Methods: Healthy subjects underwent eight different test scenarios including Valsalva maneuver, breath holding or resting in three different body positions (upright, supine or 45 degree head down tilt (HDT)) in randomized order; a separate group of healthy subjects were included in the upright resting condition only to establish repeatability of measurements of the pupillometer in our population Idiopathic intracranial hypertension subjects underwent five different test scenarios including resting in five different body positions (upright, supine, 15 HDT, 30 HDT, 45 HDT). The pupillary dynamics were automatically calculated by the pupillometer and additionally converted to a composite measure of pupillary reactivity known as the neurological pupillary index "NPI".

Results: Forty-one subjects were enrolled in the study; 30 healthy subjects, and 11 IIH. The mean age of our population was 32 years (range 22 to 49) with 66% females. In the healthy subjects (n=20), the NPI, MAX and MIN were observed to change with position. In this same population, there was also a small but statistically significant decrease in NPI observed in the upright position after breath holding. In the IIH group (n=11) the MAX, MIN and LAT had statistically significant increase with position. When comparing the healthy and IIH test populations, there were statistically significant differences observed in the upright position in the NPI, MAX, MIN, CV, MCV and DV.

Conclusions: We observed a statistically significant change in the healthy test subjects and IIH test subjects based on changes in position and task. There was also a statistically significant difference between the healthy subjects and the IIH subjects. This is consistent with our hypothesis that elevated ICP may result in decreased pupillary reactivity even in the absence of brain edema. However, the magnitude of change was small, and variable between subjects so it is unlikely that based on this initial data that this method could be used clinically without individual subject calibration.

Introduction

Recently, it was discovered that some long duration astronauts develop visual impairment and findings suggestive of elevated intracranial pressure (ICP) (Mader et al, 2011). This may be due to headward fluid shifting, carbon dioxide exposure, resistive exercise, and other unknown factors. The physiological abnormalities manifesting with ocular and intracranial structural changes associated with this condition, often referred to as Visual Impairment and Intracranial Pressure (VIIP) have yet to be clearly defined. Given that elevated ICP is considered a critical factor that may contribute to VIIP, a crucial task is to identify non-invasive methods for early detection of elevated ICP in space. These non-invasive methods are also urgently needed in many settings on Earth where invasive ICP monitoring is not possible or desirable due to risks.

It is well known that elevated ICP leads to decreased pupillary reactivity in some patients with brain injury. This is mainly based on literature from traumatic brain injury patients who have cerebral edema (Chestnut et al, 2000). In these patients, increased ICP is associated with decreased pupillary reactivity likely related to dysfunction of the anatomical pathways involved in the pupillary light reflex, from direct pressure on these structures from brain tissue shifts (i.e. brain herniation). Quantitative pupillometry can detect reduced pupillary reactivity when ICP is high in this setting (Taylor et al, 2003). Specifically, constriction velocity on the ipsilateral side of the mass defect decreased in patients with midline shift of >3 mm and an elevation in ICP for >15 minutes. In patients with cerebral edema and no midline shift the constriction velocities did not fall until the ICP >30 mm Hg. It was also observed that in a subset of patients with ICP >20 mm Hg the pupillary dynamics remained stable during the entire observation period. In another study of ICU patients, that NPI values of 3-5 correlated with an average peak ICP of 19.6 mmHg (Chen et al, 2011). This study also showed that increasing average peak ICP to be correlated with a NPI of <3 on at least one measurement.

To date, it is unknown whether changes in pupillary reactivity also occur when ICP is elevated in conditions where there is a lack of focal structural lesions or cerebral edema including head down tilt in healthy subjects, or patients with idiopathic intracranial hypertension

Head down tilt (HDT) is a well established space flight analog to study the effects of gravitational unloading on physiological systems. HDTinduces a hydrostatic gradient that increases ICP related to the height of the fluid column

Breath holding is a simple maneuver which simultaneously increases carbon dioxide, and decreases oxygen, with the results of increasing cerebral blood flow. By this method, the cerebral blood volume increases, and thus ICP transiently increases.

The Valsalva maneuver is a commonly performed task for assessment of cardiovascular function, to induce Eustachian tube patency, and transiently elevates the ICP due to inhibiting

cerebral venous outflow. In a study investigating the effect of Valsalva on ICP, systolic pressure and the cerebrovascular transmural pressure, it was observed that the Valsalva maneuver increased ICP (Haykowsky et al, 2003). In neurosurgical patients with ICP monitoring who performed bicep curls with and without Valsalva, the ICP with Valsalva was 31 +/- 14 mmHg and 16 +/- 7 mmHg without (Haykowsky et al, 2003). A different study measured CSF pressure at rest as compared to after a Valsalva maneuver. It was found that all subjects were able to elevate their CSF pressure to greater than 25 cm water, and even as high as 47 cm water (Neville and Egan, 2005).

The major goal of our study was to evaluate the effects of body position on pupillary reactivity. The secondary aim of the study was to evaluate the effects of transient physiological maneuvers including Valsalva and breath holding on pupillary reactivity. We chose these maneuvers since they are experienced by the astronauts on a daily basis during routine activities aboard the International Space Station.

Methods

The study was approved by the IRB from ***December 2014 until May 2016*** at Baylor College of Medicine, and written informed consent was obtained from all subjects prior to enrollment. Healthy volunteer subjects, men and women, between the ages of 18 and 50 years of age were enrolled in the first arm of the study. Volunteer subjects with idiopathic intracranial hypertension, male and female, between the ages of 18 and 50 were enrolled in the second phase of the study.

Include the study criteria (inclusion and exclusion criteria)

After consenting, each subject completed a short health screening questionnaire. For the healthy control subjects (n=10), there were three sets of three measurements recorded from each eye (R, L, R, L, R, L) while the subject was in the resting upright position over a thirty minute period. Each measurement was obtained in the right eye, followed by the left eye.

Experimental Conditions

For the healthy test portion of the first arm, 20 healthy test subjects were included. It was determined that a power of 84% would be achieved to detect an NPI change from 4.5 to 3.8, SD 1 from upright to 45 degrees HDT. NPI is a scalar value and ranges from 0 to 5. An NPI of 0 corresponds to an inactive pupil and 5 is fully reactive. Normal reactive pupil NPI values range from 3 to 5. The eight scenarios included the combination of three different tasks in three different positions. The order of position was randomized, and then the order of task within each position was randomized. The three positions were upright, supine and 45 degree HDT. The three tasks were resting, breath holding, and Valsalva. The Valsalva was accomplished by exhaling at 40 mmHg for 20 seconds in the supine and 45 degree HDT positions, it was not performed upright to avoid orthostatic hypotension. The IIH subjects underwent change in position and did not perform any maneuvers other than resting during measurements. The five positions were upright, supine, 15 HDT, 30 HDT and 45 HDT. Three measurements of each eye (six total) were taken immediately upon position change, and again after 3 minutes of stabilization.

Pupillometry

The NPi-100 Pupillometer (NeurOptics, Irvine, CA, USA) is handheld and performs each measurement in less than 5 seconds. The device is held up to the test subject's eye and rested on maxillary prominence. An infrared camera captures the pupil and displays an image on a digital screen with a green outline of the pupil. Upon release of the appropriate button, the device is engaged. As the pupil is tracked, a fixed light is flashed from the device and data is collected at greater than 32 frames per second for 2.7 seconds as the pupil constricts and then dilates. Measured variables include maximum pupil size (MAX), minimum pupil size (MIN), percent change in pupil size (%CH), latency of constriction (LAT), constriction velocity (CV), maximum

constriction velocity (MCV) and dilation velocity (DV). The pupillary dynamics were automatically calculated by the NPI-100 then and converted to a composite measure of pupillary reactivity known as the neurological pupillary index "NPI". All data parameters were recorded manually into an Excel workbook.

Ambient light was monitored with a digital lux meter for the duration of each experiment to ensure consistency. All measurements were recorded during the daytime, and each subject was asked to refrain from caffeine or alcohol consumption for four hours prior to testing.

Statistics

The healthy subject data was analyzed using descriptive statistics, ANOVA for repeated measures paired t-tests, using SPSS version 20 (IBM, Armonk). The IIH subject data for the IIH subjects was analyzed using the Kruskal-allis rank summary test is used to compare multiple means. The IIH subject data and the comparison between the healthy and IIH subjects was analyzed R Core Team (2013, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

There were a total of 41 study participants, including 10 healthy controls, 20 healthy test subjects, 11 IIH test subjects. The mean age of the study population was 32 years, 66% female and 56% Caucasian. The demographics of our entire study population is included in Table demographics.

Figure 1 displays the NPI data from the healthy control subjects. The spikes represent the individual measurements, the green line is the mean for each individual, and the error bars are the mean of the individual SDs. The results displayed in Figure 1 serve to demonstrate that the NPi-100 has good repeatability and is a reliable device when operated by different users. The graphical illustration clearly shows that repeated measures on each individual control subject display similar results over a period of 30 minutes. The coefficient of variation ranged from 2% to 6%.

In the healthy test population, the NPI, MAX and MIN demonstrated statistically significant changes relative to body position change during the resting condition The results are displayed in Table Healthy Test Population ONE and Table Healthy Test Population TWO. Also, the NPI was also observed to change with task when resting was compared with breath holding in the upright position. The NPI mean changed from 4.30 to 4.20 with resting as compared to breath holding, while in the upright position, which is a 2.3% change (p-value = 0.004).

In the IIH arm of the study, there were statistical differences observed in MAX, MIN, and LAT. These observations are displayed in Table IIH. MAX was observed to have a trend of increase in pupil size with decline in head position, both immediately after position change and after 3 minutes of stabilization. MIN was observed to have a trend of increase in pupil size with decline in head position after 3 minutes of stabilization. LAT was observed to have a trend of increase in time with decline in head position after 3 minutes of stabilization from supine to HDT15 and then HDT30. There was no further increase in rather it had a statistically significant decrease to a level between the value for supine and HDT15.

In the IIH population, there were no significant changes in the mean values with position or time in position for NPI, %CH, CV, MCV, and DV.

When the Welch Two Sample T-Test is was used to compare the results of the healthy test subjects with the results of the IIH test subjects, there were several significant differences noted. These included mostly results taken in the upright position. There were no significant results in comparison of the LAT. The significant differences are displayed in Table Significant Population Diffs. The mean values for each parameter reported by the NPI-100 are summarized in Table Healthy vs IIH Means.

Discussion

The main finding in our study was a statistically significant difference in various output measurements of the NPI-100 in healthy test subjects based on changes in position and task. There was also a statistically significant difference between the healthy subjects and the IIH subjects. This is consistent with our hypothesis that elevated ICP may result in decreased pupillary reactivity even in the absence of brain edema.

For the first arm of our study, it was our hypothesis that pupillary reactivity (NPI, MAX, MIN, CV and DV) would show distinct changes in healthy volunteers if they are placed in various positions and are performing various maneuvers intended to increase their ICP. We also hypothesized that performing breath holding or the Valsalva maneuver, as compared to resting, would change pupillary reactivity (NPI, MAX, MIN, CV and DV). For the second arm of the study, we hypothesized that there would be a change in pupillary reactivity with position change in IIH test subjects. We also hypothesized that there would be a significant difference in the pupillary reactivity of the healthy subjects as compared with the IIH subjects.

To our knowledge, this study provides the first known data to establish feasibility of using quantitative pupillometry to detect transient changes in ICP in healthy subjects without focal brain injury. Our underlying goal of this study was to evaluate the use of quantitative pupillometry as a potential source of non-invasive ICP measurement in order to determine if it has utility monitoring the ICP in astronauts aboard the International Space Station (ISS).

The topic of ICP has become an area of great interest for NASA and the space medicine community since the release of a case series involving seven astronauts by Mader et al in 2011. The major findings in these seven astronauts, who were all subject to long durations in microgravity, include optic disc edema, globe flattening, choroidal folds, cotton wool spots, nerve fiber layer thickening, decreased near vision and elevated intracranial pressure (Mader et al, 2011). These findings were preceded by over 300 astronauts, since 1989, documenting subjective changes in their vision either during or post-spaceflight (Mader et al, 2011).

Pupillometry is potentially useful in monitoring changes in ICP based on the anatomical pathways of nerves involved in the pupillary response. There are four different nerve cells that carry electrical signals from the eye to the brainstem, and then back from the brainstem to the eye. The light stimulus is absorbed by the retinal ganglion cells, which then transmit a stimulus via CNII to the pretectal nucleus (located in the midbrain). From the pretectal nucleus the signal is carried by axons to the Edinger-Westphal nucleus (also located in the midbrain). Parasympathetic neurons on the superficial surface of CNIII then carry a response signal from the Edinger-Westphal nucleus to the ciliary ganglion. From the ciliary ganglion, the short ciliary nerves carry the response signal to the iris sphincter muscle, which directly controls the pupil size.

Of specific interest are CNII, the pretectal nucleus, and CNIII, all of which are directly in contact with CSF. The direct contact with the CSF allows for direct compression since CSF is generally considered an incompressible fluid. Other parts of the signal pathway are within brain tissue, which provides some barrier to compression.

In attempts to track intracranial pathology, in a non-invasive manner, many devices such as the infrared pupillometer (NeurOptics Inc., Irvine CA) have been proposed. The pupillometer has been the subject of many studies including the 2003 study by Taylor et al which provides a large baseline set of healthy, at rest, measurements and an additional smaller set of distinguishable data from patients with increased ICP (Taylor et al, 2003). The device has been evaluated in many different healthcare settings including CPR prognosis (Behrends et al, 2012), autonomic assessment (Piha and Halonen, 1994; Muppidi et al, 2013), glaucoma screening (Chang et al, 2013), central cholinergic deficiency in Parkinson's disease (Stergiou et al, 2010), Alzheimer's disease diagnosis and observation (Nakou et al, 2010), and many more. In a study examining the NeurOptics pupillometer in an ICU setting, it was found that the pupillometer was more reliable than manual examination as performed by nurses, interns and neurosurgeons. Specifically, the interexaminer agreement was 39% by manual exam and 1.4% by pupillometer exam ($p < 0.001$) (Meeker et al, 2005). Thus the NeurOptics pupillometer has been the subject of a handful of recent studies as a device with still unknown potential prior to our experiment.

For contextualization of our data with the current literature, the results of common variables of our total and control population, in comparison with a select group of previous studies are listed in Table XX.

Our study had the following limitations. First the changes in nPI although significant were small in magnitude, thus may not be useful clinically. Next, the pattern of change in relation to position change was non-linear. According to our hypothesis, we expected to observe finding that would be correlated with increased ICP as the healthy test subject went from upright, to supine and then to HDT45. For example, we expected the NPI to decrease from upright to supine, and then decrease again from supine to HDT45. Similarly, we expected the MAX and MIN to increase from upright to supine, and increase again from supine to HDT45. However, the trend was not observed going from upright to supine. In fact, the mean values for NPI, MAX and MIN all went in the opposite direction as we expected when going from upright to supine. Similarly, while there were some statistically significant trends observed, the trend was not consistent with all variable and all changes in the IIH test population.

Also based on the current literature, there were three specific relationships that we expected to observed, but did not. There was no statistically significant change in the CV with the maneuvers intended to increase ICP. There was no significant relationship between age with LAT (Taylor et al, 2003; Boev et al, 2005), or MAX and CV as has been previously demonstrated (Taylor et al, 2003).

The lack of observed changes might be due to sympathetic stimulation with steeper HDT positions. We did not specifically measure markers of sympathetic activity in our study, however, previous studies have observed no changes in blood pressure or heart rate with Valsalva, deep breathing, or tilt-table positioning up to HDT30 (Piha and Halonen, 1994; Vijayalakshmi and Madanmohan, 2006). Our team also prepared each subject with demonstrations of the tilt table and the NPi-100 before testing in attempts to minimize anxiety. However, this is an area of potential autonomic confounding that should be further clarified with future studies.

In addition to potential autonomic confounding, the inability to control other factors that affect pupillary size and reactivity, such as level of alertness or sleep patterns could account for our lack of consistent findings. Multiple studies have shown that there is periodic daily variation in pupil size (Wilson et al, 2008; Kraemer et al, 2000). To try to mitigate this factor our team tested participants during the same period each day.

Additionally, our study included healthy subjects that were observed for a short period of time. Healthy subjects have compensatory mechanisms that preclude the transient changes in ICP from causing large scale changes in pupillary dynamics. The hypothesized changes might be observed in healthy subjects, but it may require longer periods of time in situations meant to increase ICP.

Further investigations are needed to confirm the degree of ICP elevation that is necessary to affect pupillary reactivity, and ideally having a direct measurement of ICP. This may be possible in some subjects who have implanted telemetric ICP probes, or access of an Ommaya reservoir. One could also consider the use of an animal model where ICP can be manipulated and monitored. It would be useful to determine whether a time dependent effect exists for the maneuvers which can be studied in a longer term bed rest study, or other ground based analogs including patients with simultaneous non-invasive or invasive ICP assessment.

Conclusions section?

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Tables and Figures

		MAX (mm)	MIN (mm)	%CH	LAT (s)	CV (mm/s)	DV (mm/s)
Larson and Muhiudeen, 1995	Post-resuscitation w/ absent subjective PLR, 150 lux	6.0 +/- 1.2	5.7 +/- 0.1	5		0.9 +/- 0.2	0.4 +/- 0.1
Taylor et al, 2003	HV at ambient light	4.1 +/- 0.34	2.7 +/- 0.21	34	0.24 +/- 0.4	1.48 +/- 0.33	
Boev et al, 2005	Healthy pediatric subjects, ambient light	4.11	2.65	36		2.34	2.2
Wilson et al, 2008	HV, morning results	4.8	3.1	32.5	0.23	2.49	1.16
	HV, evening results	5.3	3.4	35.2	0.22	2.65	1.22
Bradley et al, 2010 (range in parenthesis)	HV w/ blue eyes at 1 lux	6.13 +/- 0.6 (3.5, 8.3)					
	HV w/ blue-green eyes at 1 lux	6.55 +/- 0.5 (4.2, 8.6)					
	HV w/ green-brown eyes at 1 lux	6.29 +/- 0.6 (3.6, 8.0)					
	HV w/ light brown eyes at 1 lux	6.46 +/- 0.6 (4.4, 8.7)					
	HV with dark brown eyes at 1 lux	6.45 +/- 0.5 (4.2, 8.4)					
Behrends et al, 2012	CPR patients w/ PLR	4.3+/-1.2	3.86+/-0.3	10%			
	CPR patients w/o PLR	4.7+/-0.6	0	0%			
Theodossiadis et al, 2012	HV, right eye, ambient light	3.53 +/- 0.14	2.41 +/- 0.07	30.16 +/- 1.49	0.27 +/- 0.01	2.06 +/- 0.14	0.85 +/- 0.05
	HV, left eye, ambient light	3.56 +/- 0.14	2.42 +/- 0.08	29.48 +/- 1.71	0.26 +/- 0.01	2.05 +/- 0.16	0.85 +/- 0.06
	Tamsulosin patient, right eye, ambient light	3.03 +/- 0.14	2.27 +/- 0.11	24.93 +/- 1.87	0.28 +/- 0.01	1.36 +/- 0.12	0.77 +/- 0.05
	Tamsulosin patient, left eye, ambient light	2.94 +/- 0.14	2.24 +/- 0.13	23.67 +/- 2.16	0.28 +/- 0.01	1.36 +/- 0.15	0.75 +/- 0.05

	Alfuzosin patient, right eye, ambient light	3.04 +/- 0.10	2.24 +/- 0.06	25.95 +/- 1.59	0.28 +/- 0.01	1.52 +/- 0.12	0.79 +/- 0.06
	Alfuzosin patient, left eye, ambient light	3.08 +/- 0.11	2.25 +/- 0.05	26 +/- 1.75	0.28 +/- 0.01	1.57 +/- 0.14	0.80 +/- 0.05
Soeken et al, 2016	**HV, healthy subjects at ~ 100 lux**	**4.62 +/- 1.04**	**2.92 +/- 0.55**	**35.91 +/- 5.48**	**0.23 +/- 0.02**	**2.89 +/- 0.75**	**1.34 +/- 0.31**
	IIH subjects at ~100 lux	**5.02 +/- 1.26**	**3.25 +/- 0.84**	**34.68 +/- 6.87**	**0.23 +/- 0.02**	**3.17 +/- 0.73**	**1.44 +/- 0.31**

Table XX. Common variable comparison of mean values among various pupillometry studies.

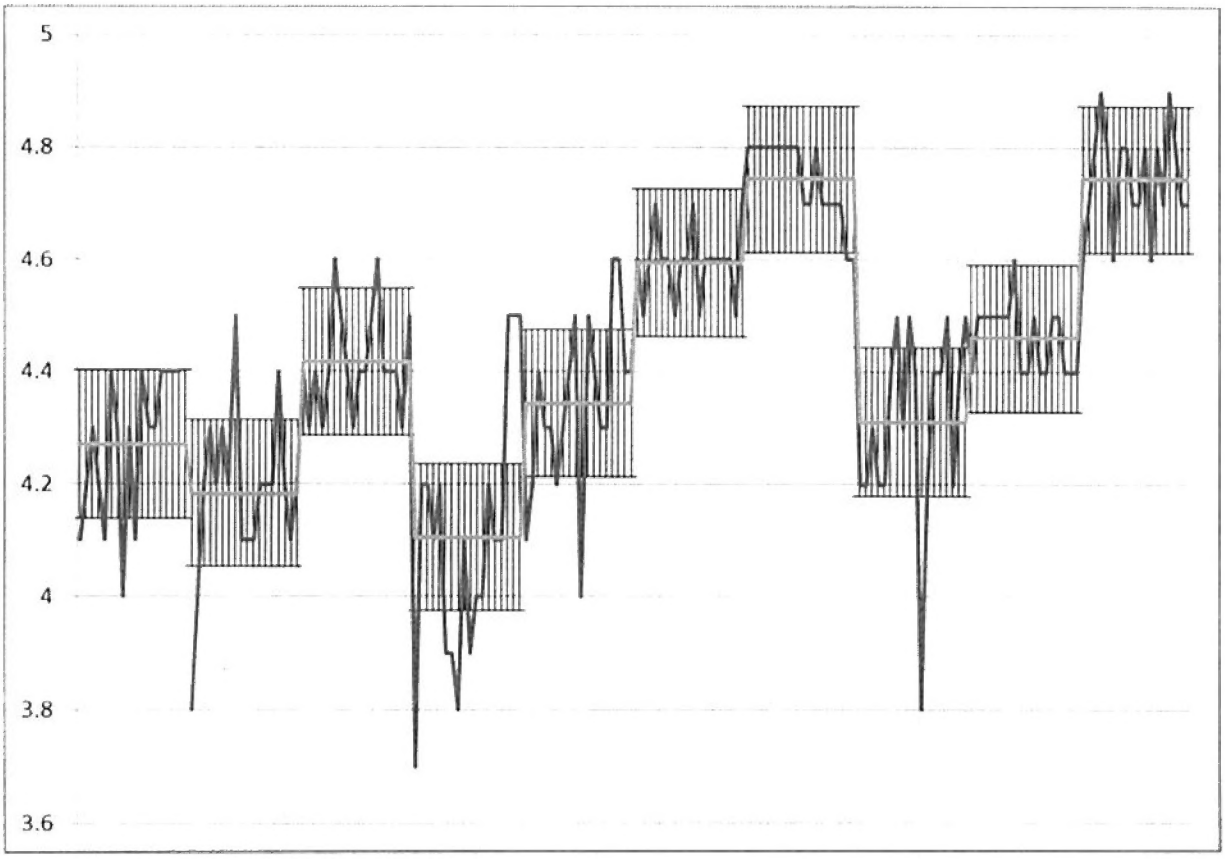

Figure 1. Control NPI Repeated Measurements with Overlaying Individual Means and Mean of Individual Standard Deviations.

	Age Range, Mean	Gender (% Female)	Caucasian	Hispanic	Asian	African American	Unspecified
Healthy Subjects, n=30	22-49, 31	57%	16	7	3	2	2

IIH Subjects, n=11	23-49, 34	91%	7	3	0	1	0
Total Study Population, n=41	22-49, 32	66%	23	10	3	3	2

Table Demographics.

Measurement	Position, Task	NPI	MAX	MIN
	Upright, Resting	4.30	4.74	3.04
	HDT45, Resting	4.12	5.19	3.44
Relative Change		4.2%	8.7%	11.6%
p-value		<0.001	0.017	<0.001

Table Healthy Test Population ONE. Statistically Significant Changes Observed in the Healthy Subjects.

Measurement	Position, Task	NPI	MAX	MIN
	Supine, Resting	4.31	4.45	2.90
	HDT45, Resting	4.12	5.19	3.44
Relative Change		4.4%	14.3%	15.7%
p-value		<0.001	<0.001	<0.001

Table Healthy Test Population TWO. Statistically Significant Changes Observed in the Healthy Subjects.

Measurement		MAX (T=0)	MAX (T=3min)	MIN (T=3min)	LAT (T=3min)
	Supine	4.47	4.35	2.92	0.216
	HDT 15	4.76	4.75	3.17	0.221
	HDT 30	4.95	4.82	3.27	0.226
	HDT 45	5.02	5.13	3.44	.0219
p-value		0.019	0.005	0.01	0.026

Table IIH. Statistically Significant Changes Observed in the IIH Subjects with change in position.

Measurement	NPI	MAX	MIN	%CH	%CH	CV	MCV	DV	DV
Position	Upright	Upright	Upright	Supine	HDT 45	Upright	Upright	Upright	HDT 45
Mean (all healthy subjects, n=30)	4.37	4.62	2.92	34.0	35.1	2.89	4.50	1.34	1.53
Mean (IIH subjects, n=11)	4.25	5.02	3.25	31.8	32.3	3.17	4.82	1.44	1.37
p-value	0.01929	0.01927	0.003086	0.0204	0.004879	0.007575	0.04689	0.0144	0.01697

Table Significant Population Diffs. Statistically Significant Differences Between Healthy Subjects and IIH Subjects.

Measurement	NPI	MAX	MIN	%CH	LAT	CV	MCV	DV
Mean (all healthy subjects, n=30)	4.37 +/- 0.30	4.62 +/- 1.04	2.92 +/- 0.55	35.91 +/- 5.48	0.23 +/- 0.02	2.89 +/- 0.75	4.50 +/- 1.13	1.34 +/- 0.31
Mean (IIH subjects, n=11)	4.25 +/- 0.40	5.02 +/- 1.26	3.25 +/- 0.84	34.68 +/- 6.87	0.23 +/- 0.02	3.17 +/- 0.73	4.82 +/- 1.22	1.44 +/- 0.31

Table Healthy vs IIH Means. Mean NPI-100 Values Comparing Healthy Subjects and IIH Subjects, Upright Position, Resting Task.